REMARKS

These remarks are in response to the Office Action mailed February 20, 2004. Claims 1,3 and 9 have been amended to further define Applicant's invention. Applicant respectfully requests consideration and allowance of the pending claims as amended.

Objections Maintained

Applicants will submit the required formal drawings when a Notice of Allowance is received.

Rejections under 35 § USC 102

Claims 1 and 3 stand rejected under 35 USC §102 (b) as allegedly being anticipated by Hoyer et al, 1998. The Office Action states that Hoyer et al. (1998) taught a composition, which comprises the purified N-terminal domain of Als1p protein of *Candida albicans* dissolved in PBS, i.e., a biocompatible carrier for injection or infusion (see pages 5336 and 5337). Applicant respectfully traverses.

Hoyer et al. describes the PCR amplification of a polynucleotide encoding a 433 amino acid N-terminal fragment of ALS1 protein. This 433 amino acid fragment was dissolved in and dialyzed against PBS (phosphate buffered saline; a common buffer for proteins) only as part of a mixture of other peptides and was solubilized for subsequent use in biochemical characterization experiments, such as electrophoresis. Hoyer et al. did not formulate the 433 amino acid fragment in an isolated and purified composition. When Hoyer et al. desired to create anti-ALS1 antibodies, they used a mixture of four, 10 mer peptides derived from conserved regions of ALS1 as antigen to produce ALS1 antiserum. This is not the isolated and purified compound of the claims. In contrast, Applicants formulated the isolated and purified N-terminal fragment of ALS1 protein together with a biocompatible carrier and used this composition (precisely what is claimed) to elicit an *in vivo*

immune response, and demonstrated that ALS1-antiserum obtained to the N-terminal region of ALS1 protein blocked the adherence of ALS1 to endothelial cells.

Not only did Hoyer et al. (1998) not use the purified 433 aa protein as an antigen to produce anti-Als antiserum, Hoyer et al. did not teach the use of the protein fragment as antigen, nor disclose the usefulness of ALS1 antiserum to block adherence of ALS1 to endothelial cells. In contrast, Applicants show data for the binding of ALS1 to endothelial cells, the identification of ALS1 as a downstream effector of filamentation and ensuing virulence, and the blocking of binding with ALS1-antiserum.

In the 1998 reference, Hoyer et al. disclosed the use of an anti-Als antiserum to test variation in length of Als proteins. Hoyer states, "This band was presumed to be the N-terminal portion of Als1p. Its identity was confirmed by Western blotting with the anti-Als antiserum described above." (p. 5336). Reading of Hoyer's materials and methods (p. 5335) shows that instead of using the 433 amino acid fragment as antigen, Hoyer used a mixture of four, 10-mer peptides as antigen to identify the location of Als proteins on Western blots.

As Hoyer describes,

> Production of anti-Als antiserum. Hyperimmune anti-Als serum raised in a New Zealand White rabbit...The anti-Als serum was raised against four 10-mer peptides derived from the N-terminal domain of Als1p. These peptides were chosen because they were likely to be in a hydrophilic, surface-exposed region of the mature, folded protein as predicted by secondary structure algorithms. Peptides from the N-terminal region of Als1p were selected because this portion of the protein was predicted to be relatively free of glycosylation compared to other regions of the protein. The peptides selected were GWSLDGTSAN (amino acids 53 to 62), FYSGEEFTTF (amino acids 98 to 107), TGSSTDLEDS (amino acids 139 to 148), and NTVTFNDGDK (amino acids 156 to 165). These peptides were linked to keyhole limpet hemocyanin (KLH) and combined in equal quantities prior to emulsification in Freund's complete adjuvant."

Thus, the antigen Hoyer used was a mixture of peptides from conserved regions common to all of the known ALS protein family. Hoyer states that these amino acid sequences were chosen because they were located in conserved region of the protein, and were likely to be surface exposed.

We performed a BLAST search on-line (see attached data) on these four peptides. We found that three of the four peptides are specific for ALS proteins, but one (NTVTFNDGDK) shows a match of 9/10 amino acids with a non-*Candida* proteins. A mixture of the four peptides used as antigen, therefore, would not be specific for ALS proteins. Clearly, this mixture is not the isolated and purified ALS protein claimed.

To summarize, the compositions disclosed in the prior art of Hoyer et al. (1998) reference are clearly distinct from the present claimed invention. Hoyer et al. used a complex mixture of peptides, not a single protein, to generate antibodies to ALS1. "Disclosure of assertedly anticipating prior art reference must be adequate to enable possession of desired subject matter, and reference that names or describes desired subject matter thus does not anticipate if subject matter cannot be produced without undue experimentation." *Elan Pharmaceuticals v. Mayo Foundation 68 USPQ2d 1373.* The disclosure in an assertedly anticipating reference must be adequate to enable possession of the desired subject matter. It is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation."

The 433 amino acid N-terminal fragment of ALS exists only in a complex mixture, not as an isolated and purified protein. This fact is most readily shown by noting that Hoyer did not prepare antibodies from the isolated and purified N-terminal region of ALS1 protein. Applicants of the present invention, however, have caused the production of a specified N-terminal region of ALS1 protein *in vivo* to elicit a specific immune response. Applicants have determined that ALS1

contributes to *Candida* virulence, and that this antiserum blocked the adherence of a *S. cerevisiae* clone containing ALS1 to endothelial cells.

For the above reasons, the present invention recites elements not disclosed by the prior art and the pending claims cannot be anticipated by Hoyer et al. (1998). For these reasons, Applicant respectfully requests the withdrawal of the 102 rejection over Hoyer (1998).

Rejection under 35 §USC 103

The Office Action alleges that Claims 1, 3 and 9 stand rejected under 35 § USC 103(a) as being unpatentable over Hoyer (1995) in view of Applicant's admitted state of the prior art. Applicant respectfully traverses this rejection.

The Office Action requests that Applicant structurally define the claimed protein fragment by molecular weight or by a specific ID number. Applicant has amended the claims to included a Sequence ID No. as requested.

The Office Action alleges that Hoyer (1995) taught the N-terminal amino acid sequence of an isolated ALS1 protein of *Candida albicans.* Applicant submits that Hoyer (1995) discloses the "complete nucleotide sequence of ALS1 from C. albincans strain B792 and **predicted** amino acid translation (emphasis added). Hoyer did not disclose amino acid analysis nor amino acid sequencing data of ALS1. Instead, Hoyer deduced the amino acid sequence from the DNA sequences of overlapping clones. In 1995, the function of ALS1 was not known.

Applicants submit that the DNA sequence alone and the predicted amino acid sequence would not enable the production of an ALS antibody that blocks endothelial binding ability. There is no data in Hoyer (1995, 1998) showing that ALS1 is a downstream effector of filamentation regulatory pathway. Thus, there is no motivation in Hoyer (1995, 1998) to make an antibody to ALS1 to block adherence. Hoyer et al. never formulate an isolated, purified protein with the carrier.

The production of antibodies is not predictable, because biological systems are highly unpredictable. It is very likely, however, that antibodies generated using a mixture of four 10-mer peptides could be expected to be different from antibodies generated using the N-terminal region of ALS1 as antigen. This is especially true given that one of the 10-mer peptides Hoyer et al. used was not 100% specific for ALS protein.

Although some kind of antibody can be produced, the desirable approach to production of the antibody for clinical application must be considered. In this instance, an expression system in *S. cerivisiae* was used to obtain correct folding and post-translational modification of the native protein used as antigen. Applicants of the present invention have disclosed the method of making such an antibody composition, and demonstrated its characteristics and usefulness.

The Examiner states that it is expected to have the intrinsic ability to produce an effective immune response in a patient. The ability to produce an effective immune response in a patient is viewed as an uncharacterized functional property of Hoyer's (1995) N-terminal protein fragment (52-1296).

As stated in MPEP §2112.01, inherency can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product (*In re Best, 562 F.2d 1252, 1255; In re Spada, 911 F.2d 705, 709)* Further, MPEP § 2112.02 states if the composition is physically the same, it must have the same properties. "Products of identical chemical composition can not have mutually exclusive properties." (*In re Spada, 911 F2d 705, 709)*

There is no identical chemical composition here. The claimed product of present invention is distinct from that of Hoyer's disclosures in 1995 and 1998. In 1995 Hoyer overlapped nucleotide sequence data from clones, and published the nucleotide sequence of the ALS1 protein and its predicted amino acid sequence (emphasis added). In 1998, Hoyer isolated a 433 amino acid

fragment of ALS1 by *in vitro* PCR technique, but did not use this fragment as antigen. Hoyer identified this fragment as related to ALS1 using antisera generated by using a mixture of four, 10 mer peptides taken from conserved regions of the ALS1 protein. The applicants of the present invention, however, generated antiserum using inoculants of *S. cerivisae* transformed with ALS1. This *in vivo* methodology insures the production of the native ALS1 protein and specific antigenicity. The fact that Hoyer had a mixture of *S. cerivisae* protein including the 433 amino acid fragment of ALS1 in PBS, a suitable carrier, is of no consequence. In 1998, Hoyer et al did not use the ALS1 fragment as antigen, nor teach the use of this ALS1 fragment to block attachment to endothelium. Rather, Hoyer teaches the use of a mixture of 10-mer peptides.

Hoyer in 1995 discloses a predicted amino acid sequence and the hypothesis that ALS antiserum would be useful to determine overall size differences in ALS proteins. There is no disclosure in Hoyer in 1995 nor in 1998 for the procedure for obtaining antibodies using portions of the ALS protein as antigen that are longer than 10 amino acids. Further, these two Hoyer references do not teach the motivation to use ALS1 antiserum to inhibit endothelial binding of *Candida* ALS proteins.

Hoyer in 1995 was interested in determining whether variation of the tandem repeats existed, and made a prophetic statement about the usefulness of antibodies to detect the size variations of ALS proteins in a Western blot. Hoyer et al. (1995) did not teach the use of the N-terminal region as an antigen. Instead, Hoyer is discussing the tandem repeat region of ALS1, and speculates that "an antiserum raised against ALS1 sequences" will establish size differences in ALS1 proteins in certain *C. albicans* strains. (See p. 49).

This revelation of planned experiments is not demonstration of an actual composition or its utility.

In summary, Applicants submit that Hoyer did not have an ALS antibody in hand in 1995. Indeed, Hoyer in 1998 only had antibodies generated by a peptide mixture of ALS protein, not to the isolated ALS protein itself.

Applicants submit that the pending claims 1, 3 and 9 and new claims 10, 11, and 12 are in condition for allowance and request such action accordingly.

The Commissioner is authorized to charge to Orrick, Herrington & Sutcliffe LLP Deposit Account No. 150665 **$55.00** for the one month extension fee. The Applicants' attorney of record hereby authorizes the Commissioner to charge any additional amounts due in the above-identified application to Orrick, Herrington & Sutcliffe's Deposit Account No. **150665** and to credit any overpayments to said Deposit Account No. **150665**.

Respectfully submitted,

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